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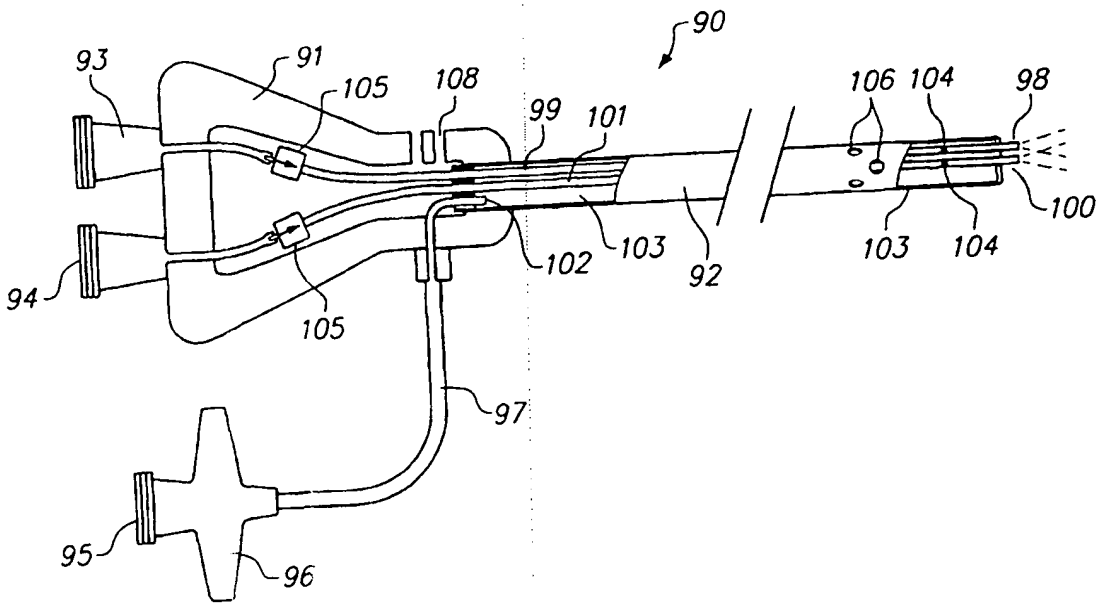

7) Abstract

Methods, and apparatus of forming in situ tissue adherent barriers are provided using a sprayer (90) capable of applying two or iscous cross linking solutions to tissue. The sprayer (90) comprises separate spray nozzles (98, 100) for each of two or more cross olutions, wherein each nozzle (98, 100) is in communication with a gas pressurized chamber (48) also may include valves (52) it back flow through the supply lines (99, 101) carrying the cross linking solutions, and a venting system (106, 108) for venting ure for laparoscopic applications. In the presence of gas flow, the cross linking solutions are atomized, and mixed to form a component hydrogel systems suitable for use with the inventive methods, and apparatus are also described.

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METHODS AND APPARATUS FOR IN SITU FORMATION OF HYDROGELS

Field Of The Invention

This present invention relates generally to methods and apparatus for forming hydrogels in situ, especially during minimally invasive surgery. More particularly, the present invention relates to apparatus and methods for delivering two liquid components that form hydrogels upon mixing.

Background Of The Invention

Often during surgery, tissue may be traumatized or compromised such that it needs to be temporarily supported or isolated during the wound healing period. Materials that may be used as tissue sealants also may be used to temporarily support tissue and to seal leaks from tissue until the tissue heals. Tissue sealants that perform these functions are well known in literature and include a variety of natural and synthetic sealants including fibrin sealants, cyanoacrylate based sealants, and other synthetic sealants and polymerizable macromers.

Various types of previously known apparatus have been developed to deliver fibrin sealants, which

are derived from blood-based proteins. For example, U.S. Patent No. 5,605,541 to Holm describes apparatus and methods for applying two or more components of a fibrin sealant. That patent describes a spray head having a central gas discharge port and coaxially arranged annular ports through which respective components of the fibrin sealant are discharged. The spray head may be prone to clogging if the central gas discharge port is restricted.

U.S. Patent No. 5,368,563 to Lonneman et al. describes a sprayer assembly having angular connecting channels through which components of a fibrin sealant are discharged to cause mixing. U.S. Patent 5,341,993 to Haber et al. describes a hand held sprayer having a remotely actuated spray tip. Both of the devices described in those patents may not be suitable for spraying viscous fluids, which tend to emerge as streams rather than as fine sprays.

U.S. Patent No. 4,001,391 to Feinstone et al. describes a method for spraying viscous and buttery fluids using a propellant and a pressurized container. The use of propellants is undesirable in medical applications due to uncertain biocompatibility of these materials.

Applicants further have determined that when attempting to use a propellant to apply materials in a laparoscopic setting, which typically is insufflated with a gas to provide a wider field of view for the clinician, the propellant can result in excessive distension of the tissue surrounding the operative site.

In addition, in the above laparoscopic context, when a sprayer is first introduced into the surgical site, for example, via a trocar tube, the

ambient pressure may inadvertently charge the supply reservoirs (if the supply lines of the sprayer are not already pressurized), thereby interfering with proper dispensing of the materials into the supply lines when the clinician attempts to operate the device.

In view of the foregoing, it would be desirable to provide apparatus and methods that enable a tissue coating comprising two or more crosslinkable fluids to be applied in situ as a spray.

It further would be desirable to provide apparatus and methods for spraying polymerizable fluids with reduced risk of clogging of the sprayer.

It also would be desirable to provide apparatus and methods that permit spraying of polymerizable fluids in a laparoscopic environment, but which adjusts the pressure in the cavity to account for the introduction of propellant from the sprayer, thereby avoiding excessive distension of the tissue surrounding the operative site.

It still further would be desirable to provide apparatus and methods that permit spraying of polymerizable fluids in a laparoscopic environment, but which prevent material reservoirs of the sprayer from being inadvertently pressurized by the backflow of insufflation gases through the supply lines.

Summary Of The Invention

In view of the foregoing, it is an object of the present invention to provide apparatus and methods that enable a tissue coating comprising two or more crosslinkable fluids to be applied in situ as a spray.

It is a further object of this invention to provide apparatus and methods for spraying

crosslinkable fluids with reduced risk of clogging of the sprayer.

It is another object of this invention to provide apparatus and methods that permit spraying of polymerizable fluids in a laparoscopic environment, but which adjusts the pressure in the cavity to account for the introduction of propellant from the sprayer, thereby avoiding excessive distension of the tissue surrounding the operative site.

It is a still further object of the present invention to provide apparatus and methods that permit spraying of polymerizable fluids in a laparoscopic environment, but which prevent material reservoirs of the sprayer from being inadvertently pressurized by the backflow of insufflation gases through the supply lines.

These and other objects of the invention are accomplished by providing a sprayer capable of applying two or more viscous crosslinkable components to tissue to form a coating that adheres to the tissue surface. For example, two crosslinkable solutions, each containing one component of a co-initiating system capable of crosslinking when mixed together, may be placed in separate chambers of the sprayer. When the sprayer is activated, the emergent spray contacts tissue, resulting in mixing and crosslinking of the two solutions to form a coating (for example a hydrogel) on the tissue surface.

In a preferred embodiment, the sprayer comprises separate spray nozzles for each of two or more crosslinkable solutions, with each nozzle surrounded by a separate or common gas flow outlet. The crosslinkable solutions are stored in separate compartments, e.g., a multi-cylinder syringe, and

communicated under pressure to the spray nozzles. In the presence of gas flow through the gas flow outlets, the crosslinkable solutions are atomized and mixed in the gas flow to form a spray, which may be used to coat tissue. In an alternative embodiment, the gas flow is mixed with the crosslinkable solutions to both propel the solutions out of the spray nozzles and atomize the solutions.

To avoid excessive distention of the tissue cavity surrounding the operative site in laparoscopic applications, the sprayer preferably includes a vent system that vents excess pressure from the tissue cavity. In addition, to avoid backflow into the compartments storing the crosslinkable solutions when the sprayer is first introduced into an insufflated tissue cavity, the supply lines preferably include one-way valves that permit flow through the supply line in the distal direction, but prevent backflow.

The crosslinkable solutions used with the apparatus may be crosslinked using either physical crosslinking, chemical crosslinking, or both. For a chemical initiation process, the two or more crosslinkable solutions may polymerize when mixed in the gas flows during spraying, thus forming an adherent coating that adheres to the tissue surface on contact. If a thermal initiating process is used, the two or more solutions may crosslink after contacting the tissue surface and warming to physiological temperatures.

Alternatively, the two or more solutions may include macromers that contain groups that demonstrate activity towards other functional groups such as amines, imines, thiols, carboxyls, isocyanates, urethanes, amides, thiocyanates, hydroxyls, etc., which

may be naturally present in, on, or around tissue or may be optionally provided in the region as part of the instilled formulation required to effect the barrier.

Methods of forming tissue adherent barriers in accordance with the principles of the present invention also are provided.

Brief Description Of The Drawings

Further features of the invention, its nature and various advantages will be more apparent from the accompanying drawings and the following detailed description of the preferred embodiments, in which:

FIGS. 1A, 1B and 1C, are, respectively, a perspective view of a two-fluid sprayer of the present invention, a detailed view of the distal end of the sprayer, and an end view of the distal end of the sprayer taken along line 1C--1C of FIG. 1A;

FIG. 1D is an end view of the distal end of an alternative embodiment of the sprayer of FIG. 1A taken along line 1C--1C;

FIGS. 2A, 2B and 2C, are, respectively, a perspective view of an alternative embodiment of the two-fluid sprayer of the present invention, a detailed view of the distal end of the sprayer, and an end view of the distal end of the sprayer taken along line 2C--2C of FIG. 2A;

FIG. 2D is an end view of the distal end of an alternative embodiment of the sprayer of FIG. 2A taken along line 2C--2C;

FIGS. 3A and 3B, are respectively, a partially cut-away side and a sectional end view of an alternative embodiment suitable for use in laparoscopic applications; and

FIGS. 4A and 4B, are respectively, a partially cut-away side and a sectional end view of a further alternative embodiment suitable for use in laparoscopic applications.

Detailed Description Of The Invention

The present invention is directed to the use of multi-component crosslinkable solutions to form protective coatings on tissue, e.g., to prevent post-surgical adhesions, or as drug delivery layers. In accordance with the methods of the present invention, two or more crosslinkable solutions are sprayed onto tissue during, or near the completion, of surgery to form adherent coatings.

The following written description describes multi-component hydrogel systems suitable for such use, apparatus for dispensing such hydrogel systems, and provides an illustrative example of use of the inventive methods and apparatus.

Hydrogel Systems Suitable For Use

Crosslinkable solutions preferred for use in accordance with the principles of the present invention include those that may be used to form coatings on tissue, and may form physical crosslinks, chemical crosslinks, or both. Physical crosslinks may result from complexation, hydrogen bonding, desolvation, Van der Waals interactions, ionic bonding, etc., and may be initiated by mixing two components that are physically separated until combined in situ, or as a consequence of a prevalent condition in the physiological environment, such as temperature, pH, ionic strength, etc. Chemical crosslinking may be accomplished by any of a number of mechanisms, including free radical

polymerization, condensation polymerization, anionic or cationic polymerization, step growth polymerization, etc.

Hydrogels suitable for use in accordance with the principles of the present invention preferably crosslink spontaneously without requiring the use of a separate energy source. Such systems allow good control of the crosslinking process, because gelation does not occur until the sprayer is actuated and mixing of the two solutions takes place. If desired, one or both crosslinkable solutions may contain dyes or other means for visualizing the hydrogel coating. Alternatively, a colored compound may be produced as a byproduct of the reactive process. The crosslinkable solutions also may contain a bioactive drug or therapeutic compound that is entrapped in the resulting coating, so that the coating becomes a drug delivery layer.

Properties of the hydrogel system, other than crosslinkability, preferably should be selected according to the intended application. For example, if the sprayer is to be used to provide a tissue adherent coating in the abdominal cavity to prevent post-surgical tissue adhesion, it is preferable that the hydrogel system have a relatively low tensile strength, to avoid adversely effecting normal physiologic processes of the organs, be near equilibrium hydration when formed, experience relatively little in situ swelling, and be biodegradable.

Other applications may require different characteristics of the hydrogel system. There is extensive literature describing the formulation of crosslinkable coating materials for particular medical applications, which formulae may be readily adapted for

use herein with little experimentation. More generally, for example, if a hydrogel system is to be used for coating of tissues, cells, medical devices, or capsules, for drug delivery or as mechanical barriers or supports, the materials should be selected on the basis of exhibited biocompatibility and lack of toxicity. For all biologically-related uses, toxicity must be low or absent in the finished state for externally coated non-living materials, and at all stages for internally-applied materials.

Additionally, the hydrogel system solutions should not contain harmful or toxic solvents. Preferably, the solutions are substantially soluble in water to allow application in a physiologically-compatible solution, such as buffered isotonic saline. Water-soluble coatings may form thin films, but more preferably form three-dimensional gels of controlled thickness. It is also preferable in cases that the coating be biodegradable, so that it does not have to be retrieved from the body. Biodegradability, as used herein, refers to the predictable disintegration of the coating into molecules small enough to be metabolized or excreted under normal physiological conditions.

Polymers Suitable for Physical Crosslinking

Physical crosslinking may be intramolecular or intermolecular or in some cases, both. For example, hydrogels can be formed by the ionic interaction of divalent cationic metal ions (such as Ca+2 and Mg+2) with ionic polysaccharides such as alginates, xanthan gums, natural gum, agar, agarose, carrageenan, fucoidan, furcellaran, laminaran, hypnea, eucheuma, gum arabic, gum ghatti, gum karaya, gum tragacanth, locust beam gum, arabinogalactan, pectin, and amylopectin.

These crosslinks may be easily reversed by exposure to species that chelate the crosslinking metal ions, for example, ethylene diamine tetraacetic acid. Multifunctional cationic polymers, such as poly(l-lysine), poly(allylamine), poly(ethyleneimine), poly(guanidine), poly(vinyl amine), which contain a plurality of amine functionalities along the backbone, may be used to further induce ionic crosslinks.

Hydrophobic interactions are often able to induce physical entanglement, especially in polymers, that induces increases in viscosity, precipitation, or gelation of polymeric solutions. For example, poly(oxyethylene)-poly(oxypropylene) block copolymers, available under the trade name of PLURONIC®, BASF Corporation, Mount Olive, NJ, are well known to exhibit a thermoreversible behavior in solution. Thus, an aqueous solution of 30% PLURONIC® F-127 is a relatively low viscosity liquid at 4°C and forms a pasty gel at physiological temperatures due to hydrophobic interactions. Other block and graft copolymers of water soluble and insoluble polymers exhibit similar effects, for example, copolymers of poly(oxyethylene) with poly(styrene), poly(caprolactone), poly(butadiene) etc.

Techniques to tailor the transition temperature, i.e. the temperature at which an aqueous solution transitions to a gel due to physical linking, are per se known. For example, the transition temperature may be lowered by increasing the degree of polymerization of the hydrophobic grafted chain or block relative to the hydrophilic block. Increase in the overall polymeric molecular weight, while keeping the hydrophilic: lipophilic ratio unchanged also leads to a lower gel transition temperature, because the

polymeric chains entangle more effectively. Gels likewise may be obtained at lower relative concentrations compared to polymers with lower molecular weights.

Solutions of other synthetic polymers such as poly(N-alkylacrylamides) also form hydrogels that exhibit thermoreversible behavior and exhibit weak physical crosslinks on warming. During spraying of thermoreversible solutions, cooling of the solutions may be expected from evaporation during atomization. Upon contact with tissue target at physiological temperatures, viscosity is expected to increase from the formation of physical crosslinks. Similarly, pH responsive polymers that have a low viscosity at acidic or basic pH may be employed, and exhibit an increase in viscosity upon reaching neutral pH, for example, due to decreased solubility.

For example, polyanionic polymers such as poly(acrylic acid) or poly(methacrylic acid) possess a low viscosity at acidic pHs that increases as the polymers become more solvated at higher pHs. The solubility and gelation of such polymers further may be controlled by interaction with other water soluble polymers that complex with the polyanionic polymers. For example, it is well known that poly(ethylene oxides) of molecular weight over 2,000 dissolve to form clear solutions in water. When these solutions are mixed with similar clear solutions of poly(methacrylic acid) or poly(acrylic acid), however, thickening, gelation, or precipitation occurs depending on the particular pH and conditions used (for example see Smith et al., "Association reactions for poly(alkylene oxides) and poly(carboxylic acids)," *Ind. Eng. Chem.*, 51:1361 (1959). Thus, a two component aqueous solution

system may be selected so that the first component (among other components) consists of poly(acrylic acid) or poly(methacrylic acid) at an elevated pH of around 8-9 and the other component consists of (among other components) a solution of poly(ethylene glycol) at an acidic pH, such that the two solutions on being combined in situ result in an immediate increase in viscosity due to physical crosslinking.

Physical gelation also may be obtained in several naturally existing polymers too. For example gelatin, which is a hydrolyzed form of collagen, one of the most common physiologically occurring polymers, gels by forming physical crosslinks when cooled from an elevated temperature. Other natural polymers, such as glycosaminoglycans, e.g., hyaluronic acid, contain both anionic and cationic functional groups along each polymeric chain. This allows the formation of both intramolecular as well as intermolecular ionic crosslinks, and is responsible for the thixotropic (or shear thinning) nature of hyaluronic acid. The crosslinks are temporarily disrupted during shear, leading to low apparent viscosities and flow, and reform on the removal of shear, thereby causing the gel to reform.

Macromers Suitable for Chemical Crosslinking

Water soluble polymerizable polymeric monomers having a functionality >1 (i.e., that form crosslinked networks on polymerization) and that form hydrogels are referred to hereinafter as "macromers". Several functional groups may be used to facilitate chemical crosslinking reactions. When these functional groups are self condensible, such as ethylenically unsaturated functional groups, the crosslinker alone is

sufficient to result in the formation of a hydrogel, when polymerization is initiated with appropriate agents. Where two solutions are employed, each solution preferably contains one component of a co-initiating system and crosslink on contact. The solutions are stored in separate compartments of a sprayer, and mix either when sprayed or on contact with the tissue.

An example of an initiating system suitable for use in the present invention is the combination of a peroxygen compound in one solution, and a reactive ion, such as a transition metal, in another. Other means for polymerization of macromers to coatings on tissue also may be advantageously used with macromers that contain groups that demonstrate activity towards functional groups such as amines, imines, thiols, carboxyls, isocyanates, urethanes, amides, thiocyanates, hydroxyls, etc., which may be naturally present in, on, or around tissue. Alternatively, such functional groups optionally may be provided in the region as part of the instilled formulation required to effect the barrier. In this case, no external initiators of polymerization are needed and polymerization proceeds spontaneously when two complementary reactive functional groups containing moieties interact at the application site.

Preferred hydrogel systems are those biocompatible multi-component systems that spontaneously crosslink when the components are mixed, but wherein the two or more components are individually stable for the duration of the deposition process. Such systems include, for example, contain macromers that are di or multifunctional amines in one component and di or multifunctional oxirane containing moieties

in the other component. Other initiator systems, such as components of redox type initiators, also may be used. The mixing of the two or more solutions may result in either an addition or condensation polymerization that further leads to the formation of a coating.

Any monomer capable of being crosslinked to form a biocompatible surface coating may be used. The monomers may be small molecules, such as acrylic acid or vinyl caprolactam, larger molecules containing polymerizable groups, such as acrylate-capped polyethylene glycol (PEG-diacrylate), or other polymers containing ethylenically-unsaturated groups, such as those of U.S. Patent No. 4,938,763 to Dunn et al, U.S. Patent Nos. 5,100,992 and 4,826,945 to Cohn et al, U.S. Patent Nos. 4,741,872 and 5,160,745 to De Luca et al., or U.S. 5,410,016 to Hubbell et al.

Preferred monomers are the crosslinkable, biodegradable, water-soluble macromers described in U.S. Patent No. 5,410,016 to Hubbell et al, which is incorporated herein by reference. These monomers are characterized by having at least two polymerizable groups, separated by at least one degradable region. When polymerized in water, they form coherent gels that persist until eliminated by self-degradation. In the most preferred embodiment, the macromer is formed with a core of a polymer that is water soluble and biocompatible, such as the polyalkylene oxide polyethylene glycol, flanked by hydroxy acids such as lactic acid, having acrylate groups coupled thereto. Preferred monomers, in addition to being biodegradable, biocompatible, and non-toxic, also will be at least somewhat elastic after polymerization or curing.

It has been determined that monomers with longer distances between crosslinks are generally softer, more compliant, and more elastic. Thus, in the polymers of Hubbell, et al., increased length of the water-soluble segment, such as polyethylene glycol, tends to enhance elasticity. Molecular weights in the range of 10,000 to 35,000 of polyethylene glycol are preferred for such applications, although ranges from 3,000 to 100,000 also are useful.

In addition, coatings formed in accordance with the methods of the present invention may be formed as laminates (i.e., having multiple layers). Thus, for example, a lower layer of the laminate may consist of a more tightly crosslinked hydrogel that provides good adherence to the tissue surface and serves as a substrate for an overlying compliant coating to reactively bond thereto. Materials having lower molecular weights between crosslinks may be suitable for use as a base coating layer. Molecular weights in the range of 400 to 20,000 of polyethylene glycol are preferred for such applications, although ranges from 400 to 10,000 are more preferable.

It should be understood, however, that hydrogels that crosslink by a variety of other mechanisms, for example, by interaction of electrophilic and nucleophilic functional groups, also may be advantageously used in accordance with the principles of the present invention.

Initiating Systems

Metal ions may be used either as an oxidizer or a reductant in redox initiating systems. For example, in the Example set forth hereinbelow, ferrous ions are used in combination with a peroxide or

hydroperoxide to initiate polymerization, or as parts of a polymerization system. In this case, the ferrous ions serve as a reductant. In other previously known initiating systems, metal ions serve as an oxidant.

For example, the ceric ion (4+ valence state of cerium) interacts with various organic groups, including carboxylic acids and urethanes, to remove an electron to the metal ion, and leave an initiating radical behind on the organic group. In such a system, the metal ion acts as an oxidizer. Potentially suitable metal ions for either role are any of the transition metal ions, lanthanides and actinides, which have at least two readily accessible oxidation states.

Preferred metal ions have at least two states separated by only one difference in charge. Of these, the most commonly used are ferric/ferrous; cupric/cuprous; ceric/cerous; cobaltic/cobaltous; vanadate V vs. IV; permanganate; and manganic/manganous. Peroxygen containing compounds, such as peroxides and hydroperoxides, including hydrogen peroxide, t-butyl hydroperoxide, t-butyl peroxide, benzoyl peroxide, cumyl peroxide, etc., may be used.

Thermal initiating systems may be used rather than the redox-type systems described hereinabove. Several commercially available low temperature free radical initiators, such as V-044, available from Wako Chemicals USA, Inc., Richmond, VA, may be used to initiate free radical crosslinking reactions at body temperatures to form hydrogel coatings with the aforementioned monomers.

Preferred macromers for use in forming tissue coatings using the apparatus of the present invention include any of a variety of in situ crosslinkable

macromers that form hydrogel compositions in vivo. These macromers may, for example, be selected from compositions that are biodegradable, crosslinkable, and substantially water soluble macromers comprising at least one water soluble region, at least one degradable region, and statistically more than 1 polymerizable region on average per macromer chain, wherein the polymerizable regions are separated from each other by at least one degradable region. Alternatively, if biodegradability is not desirable, compositions that do not contain the biodegradable segments but are substantially water soluble and crosslink in vivo under acceptable physiological conditions may be used.

Sprayers For Dispensing Hydrogel Coatings

Referring now to FIGS. 1A, 1B and 1C, an illustrative embodiment of a sprayer constructed in accordance with the principles of the present invention is described. Sprayer 10 comprises body 11 having elongated barrel 12, syringes 13 and 14, actuator 15 and gas inlet port 16 coupled to compressor 17 via flexible hose 18. Distal end 19 of sprayer 10 includes outlet nozzles 20a and 20b surrounded by gas flow outlets 21a and 21b, respectively. Compressor 17 supplies a gas flow, preferably compressed air or carbon dioxide, to sprayer 10 either continuously, or when activated by footpedal 22. Gas inlet port 16 may include filter 16a to remove particulate contaminants, including bacteria and other microorganisms, from the gas flow.

Body 11 includes compartments 23 into which syringes 13 and 14 are placed so that the outlets of the syringes are coupled in fluid communication with the interior of tubes 24 and 25, respectively. Each of

syringes 13 and 14 includes plunger 26 that may be engaged in recesses 27 of actuator 15. Accordingly, when actuator 15 is depressed, an equal volume of crosslinkable solution is dispensed from each of syringes 13 and 14. Alternatively, for some systems it may be desirable to omit actuator 15 and instead spray the crosslinkable solutions onto the tissue in a sequential fashion. In either case, sterile crosslinkable solutions may be stored separately in syringes 13 and 14, and assembled in sprayer 10 as required for a particular application.

Tube 24 extends from the proximal end of barrel 12, where it is coupled to syringe 13, to a point a slightly beyond distal endface 28 of barrel 12, where it forms outlet nozzle 20a. Tube 24 is disposed within lumen 29 that communicates with gas inlet port 16. Gas entering sprayer 10 via gas inlet port 16 flows through the annular space defined by the exterior of tube 24 and the interior surface of lumen 29, exiting sprayer 10 through gas flow outlet 21a. As the gas, preferably air or carbon dioxide, flows through gas flow outlet 21a, it mixes with the crosslinkable solution from syringe 13 passing through outlet nozzle 20a, breaking the crosslinkable solution into fine droplets or a mist.

Likewise, tube 25 extends from the proximal end of barrel 12, where it is coupled to syringe 14, to a point a slightly beyond distal endface 28 of barrel 12, where it forms outlet nozzle 20b. Tube 25 is disposed within lumen 30 that communicates with gas inlet port 16. Thus, gas entering sprayer 10 via gas inlet port 16 flows through the annular space defined by the exterior of tube 25 and the interior surface of lumen 30, exiting sprayer 10 through gas flow outlet

21b. As the gas flows through gas flow outlet 21b, it mixes with the crosslinkable solution from syringe 14 passing through outlet nozzle 20b, also breaking the crosslinkable solution into fine droplets or a mist.

Outlet nozzles 20a and 20b are preferably arranged so that the crosslinkable droplets or mist formed by outlet nozzle 20a and gas flow outlet 21a converges with that formed by outlet nozzle 20b and gas flow outlet 21b to provide a spray containing a mixture of the two crosslinkable solutions. As described hereinabove, the two solutions may either crosslink on contact within the spray, or crosslink upon contacting the tissue. Outlet nozzles 20a and 20b may extend several millimeters beyond distal endface 28 of barrel 12 to prevent clogging of the nozzles by premature crosslinking of the emergent fluids by cross-contamination.

Alternatively, it may be desirable to have outlet nozzles 20a and 20b approximately even with distal endface 28 of barrel 12 to reduce the gas flow rate required to entrain and atomize the solutions. Accordingly, outlet nozzles 20a and 20b and gas flow outlets 21a and 21b may be configured so that the movement of the gas flows from gas flow outlets 21a and 21b cause the crosslinkable solutions to be drawn out of nozzles 20a and 20b and entrained in the gas flows by a Venturi effect. In this case, no manual actuation or compression of the crosslinkable solutions is required, and plungers 26 and actuator 15 may be omitted. As a further alternative, instead of using footpedal 22 to regulate the gas flow, compressor 17 may be regulated with a valve (not shown) disposed on body 11 or barrel 12, that selectively diverts gas flow from lumens 29 and 30. This feature may be

particularly useful when the sprayer is used in closed relatively fluid tight cavities, such as the pneumoperitoneum created during laparoscopic or pelvic surgery.

Body 11, barrel 12 and actuator 15 preferably are constructed from a plastic such a polyethylene, while tubes 24 and 25 preferably comprise a rigid material, such as stainless steel. Syringes 13 and 14 may comprise materials typically used in medical devices, while compressor 17 and flexible hose 18 may be of the type commercially available, for example, that are used with airbrushes.

In operation, sprayer 10 is coupled to compressor 17 via flexible hose 18. Syringes 13 and 14 are inserted into compartments 23 of body 11 and plungers 26 of syringes 13 and 14 are engaged in recesses 27 in actuator 15. Distal end 19 of sprayer 10 is disposed within a body cavity, for example, intraoperatively in the abdomen or laparoscopically in the pneumoperitoneum, a few inches from tissue to be coated. Footpedal 22 is then depressed to activate compressor 17, while actuator 15 is depressed to dispense crosslinkable solutions from outlet nozzles 20a and 20b. As the solutions emerge from nozzles 20a and 20b, they are atomized and partially or completely mixed, and directed onto the tissue to be coated. As a result of crosslinking, for example, induced by free radical or chemical crosslinking, the solutions form a film that adheres to the tissue to provide a therapeutic benefit. Alternatively, the solutions may be mixed when they contact the tissue surface.

In FIG. 1D, an alternative embodiment is depicted in which barrel 12' includes outlet nozzles 20a' and 20b' disposed within single gas flow outlet

21a' and gas flow lumen 29'. Operation of this alternative embodiment is similar to that described hereinabove, except that the crosslinkable solutions are entrained from outlet nozzles 20a' and 20b' by a single stream of gas exiting gas flow outlet 21a'. In addition, the sprayer may include a valve or valves (not shown) for regulating the amount of crosslinkable solution and gas existing outlet nozzles 20a', 20b' and 21a', respectively. Such valves also may permit a jet of gas to be directed onto a targeted tissue, for example, to displace saline or body fluids to dry or clean the target tissue prior to instillation of the hydrogel barrier.

Referring now to FIGS. 2A, 2B and 2C, an alternative embodiment of a sprayer of the present invention for forming adherent tissue coatings from a three-part hydrogel system is described. Sprayer 40 comprises body 41 having elongated barrel 42, syringes 43, 44 and 45, actuator 46 and gas inlet port 47 coupled compressed gas cylinder 48. Distal end 49 of sprayer 40 includes outlet nozzles 50a, 50b and 50c surrounded by gas flow outlets 51a, 51b and 51c, respectively. Compressed gas cylinder 48 is coupled to gas inlet port 47 via valve 52 and filter 53. Valve 52 is configured, for example, so that it may be selectively opened or closed by rotating the valve a half-turn. Filter 53 serves the same functions as filter 16a in the embodiment of FIGS. 1.

Body 41 includes compartments 54 into which syringes 43, 44 and 45 are placed so that the outlets of the syringes are coupled in fluid communication with tubes 55, 56 and 57, respectively. Each of syringes 43-45 includes plunger 58 that may be engaged in recesses 59 of actuator 46. Actuator 46 may link all

three of plungers 58 together for common motion, or may be used to link only two of the plungers together, as illustrated by the dotted line in FIG. 2A. Actuator 46 may therefore be depressed to dispense equal volumes of crosslinkable solution from each of syringes 43-45 or just a subset thereof. As in the embodiment of FIG. 1A, the construction of sprayer 40 permits the sterile crosslinkable solutions to be stored separately in syringes 43-45, and assembled in sprayer 40 as required for a particular application.

Tube 55 extends from the proximal end of barrel 42, where it is coupled to syringe 43, to a point a slightly beyond distal endface 60 of barrel 42, where it forms outlet nozzle 50a. Tube 55 is disposed within lumen 61 that communicates with gas inlet port 47. Gas entering sprayer 40 via gas inlet port 47 flows through the annular space defined by the exterior of tube 55 and the interior surface of lumen 61, exiting sprayer 40 through gas flow outlet 51a. As the gas, preferably air or carbon dioxide, flows through gas flow outlet 51a, it mixes with the crosslinkable solution from syringe 43 passing through outlet nozzle 50a, and atomizes the crosslinkable solution into fine droplets or a mist. Tube 56, disposed in lumen 62, and tube 57, disposed in lumen 63, are similarly arranged to atomize crosslinkable solutions from syringes 44 and 45 in the gas flows exiting gas flow outlets 51b and 51c.

Outlet nozzles 50a-50c are preferably arranged so that the atomized crosslinkable solutions converge to provide a spray containing a mixture of the crosslinkable solutions. As in the previous embodiment, outlet nozzles 50a-50c preferably extend several millimeters beyond distal endface 60 of barrel

42 to prevent clogging of the nozzles by premature crosslinking of the emergent fluids by cross-contamination. Alternatively, outlet nozzles 50a-50c and gas flow outlets 51a-51c may be configured so that the gas exiting gas flow outlets 51a-51c cause the crosslinkable solutions to be drawn out of the nozzles by a Venturi effect, as described hereinabove.

With respect to FIG. 2D, an alternative embodiment is depicted in which barrel 42' includes outlet nozzles 50a', 50b' and 50c' disposed within single gas flow outlet 51a' and gas flow lumen 61'. Operation of this alternative embodiment is similar to that described hereinabove, except that the crosslinkable solutions are entrained from outlet nozzles 50a', 50b' and 50c' by a single stream of gas exiting gas flow outlet 51a'. In addition, like the embodiment described with respect to FIG. 1D, the sprayer may include a valve or valves for regulating the amount of crosslinkable solution and gas existing the outlet nozzles, and also may permit a jet of gas to be directed onto a targeted tissue to displace saline or body fluids, thereby drying or cleaning the target tissue prior to instillation of the hydrogel barrier.

The embodiments of FIGS. 2 may be advantageously used to dispense a three component hydrogel system to form an adherent therapeutic layer on a tissue surface. Alternatively, syringes 43 and 44 may contain components of crosslinkable solution that are activated to initiate crosslinking by mixing the two solutions. Syringe 45 may then contain a further crosslinkable solution that enhances adherence of the coating to tissue, for example, by providing a highly crosslinked network as the base coat or by helping the

top coat adhere better to the tissue surface by other mechanisms.

Referring now to FIGS. 3A and 3B, a further alternative embodiment of the sprayer of the present invention is described which is adapted for use in laparoscopic applications. Sprayer 70 comprises body 71 having elongated barrel 72, material supply ports 73 and 74, an actuator (not shown) and gas inlet port 75 coupled to a source of compressed gas or a compressor (not shown) via filter 76 and flexible hose 77. Supply port 73 is coupled to nozzle 78 by supply line 79 while supply port 74 is coupled to nozzle 80 by supply line 81. Gas inlet port 75 is coupled by hose 77 to nozzle 82 disposed in chamber 83. Gas exiting nozzle 82 flows into chamber 83, and then exits chamber 83 by flowing through annular gaps 84 surrounding nozzles 78 and 80, as for the embodiment of FIG. 1.

Reservoirs of crosslinkable solutions are coupled to supply ports 73 and 74, so that when sprayer 70 is actuated, compressed gas flowing around nozzles 78 and 80 draws the crosslinkable solutions through supply lines 79 and 81. The gas flow exiting through annular gaps 84 atomizes and mixes the crosslinkable solution, and deposits the crosslinkable solutions onto a target tissue.

In accordance with one aspect of the present invention, one-way valves 85 are disposed on supply lines 79 and 81 to prevent backflow of insufflation gases in a tissue cavity from charging the reservoirs of crosslinkable solutions. More specifically, one-way valves permit flow through the supply lines from the reservoirs to nozzles 78 and 80, but prevent the backflow of insufflation gases in a tissue cavity from flowing into the reservoirs when the sprayer is first

introduced into the tissue cavity. Additionally, one-way valves prevent compressed gas from the sprayer from being directed through the supply lines if, for example, if the distal end of the sprayer were pushed into tissue or otherwise blocked.

During laparoscopic surgery, for example, in the peritoneal cavity, it is typical to employ an insufflator to create a gas-filled cavity in which the surgeon can view and manipulate his or her instruments. Such devices inject a pressurized gas, such as carbon dioxide, and monitor and regulate the insufflation pressure by adding additional carbon dioxide to compensate for any leakage. Once a patient is insufflated, experienced surgeons typically maintain the insufflation without requiring much additional carbon dioxide.

Because the methods and apparatus of the present invention employ a pressurized gas to atomize and deposit the crosslinkable solution, however, a vent system must be provided to prevent excessive distension of the tissue cavity. Accordingly, sprayer 70 includes one or more vent holes 86 that communicate with bore 87 of elongated barrel 72 and proximal vent holes 88 in body 71. Vent holes 86 and proximal holes 88 permit excess gas pressure to be vented from the tissue cavity through the sprayer. While carbon dioxide will leak from the peritoneal cavity through vent holes 86 and 88, when there is no gas flow from the sprayer, applicants do not expect this leakage to present a problem, because the insufflator will add additional carbon dioxide to compensate for this leakage.

In operation, sprayer 70 is coupled to a source of compressed gas or a compressor via filter 76 and hose 77. Reservoirs of crosslinkable solutions are

coupled to supply ports 73 and 74. The distal end of sprayer 70 then is disposed within a body cavity, for example, intraoperatively in the abdomen or laparoscopically in the pneumoperitoneum, a few inches from tissue to be coated. When sprayer 70 is actuated, for example, by a footpedal (not shown) coupled to the compressor or source of compressed gas, crosslinkable solutions from nozzles 78 and 80 by gas exiting through annular gaps 84. As the solutions emerge from nozzles 78 and 80, they are atomized and mixed, and directed onto the tissue to be coated. As a result of crosslinking, for example, induced by free radical or chemical crosslinking, the solutions form a film that adheres to the tissue to provide a therapeutic benefit.

Referring to FIGS. 4A and 4B, another alternative laparoscopic embodiment of the sprayer of the present invention is described. Sprayer 90 comprises body 91 having elongated barrel 92, material supply ports 93 and 94, an actuator (not shown) and gas inlet port 95 coupled to a source of compressed gas or a compressor (not shown) via filter 96 and flexible hose 97. Supply port 93 is coupled to nozzle 98 by supply line 99 while supply port 94 is coupled to nozzle 100 by supply line 101. Gas inlet port 95 is coupled by hose 97 to outlet 102 disposed in chamber 103. Gas exiting outlet 102 flows into chamber 103 and then exits chamber 103 by flowing through openings 104 into supply lines 99 and 101.

Reservoirs of crosslinkable solutions are coupled to supply ports 93 and 94, so that when sprayer 90 is actuated, gas introduced into chamber 103 enters supply lines 99 and 101 through openings 104, mixes with and atomizes the crosslinkable solutions in the supply lines, and propels the solutions to exit through

nozzles 98 and 100. As the gas flow and solution mixture exits through nozzles 98 and 100, it further atomizes and mixes the crosslinkable solutions, and deposits the solutions onto a target tissue.

As for the embodiment of FIGS. 3, one-way valves 105 are disposed on supply lines 99 and 101 to prevent backflow of gas from chamber 103 or insufflation gases in a tissue cavity from charging the reservoirs of crosslinkable solutions. More specifically, one-way valves permit flow through the supply lines from the reservoirs to nozzles 98 and 100, but prevent the backflow of insufflation gases in a tissue cavity from flowing into the reservoirs when the sprayer is first introduced into the tissue cavity. Additionally, one-way valves prevent compressed gas from chamber 103 of the sprayer from being directed through the supply lines if, for example, if the distal end of the sprayer were pushed into tissue or otherwise blocked.

In addition, sprayer 90 includes one or more vent holes 106 that communicate via tubing 107 disposed within elongated barrel 92 and proximal vent holes 108 in body 91. Vent holes 106 and proximal holes 108 permit excess gas pressure to be vented from the tissue cavity through the sprayer. While carbon dioxide will leak from the peritoneal cavity through vent holes 106 and 108 when there is no gas flow from the sprayer, applicants do not expect this leakage to present a problem, because the insufflator will add additional carbon dioxide to compensate for this leakage.

In operation, sprayer 90 is coupled to a source of compressed gas or a compressor via filter 96 and hose 97. Reservoirs of crosslinkable solutions are coupled to supply ports 93 and 94. The distal end of

sprayer 90 then is disposed within a body cavity, for example, intraoperatively in the abdomen or laparoscopically in the pneumoperitoneum, a few inches from tissue to be coated. When sprayer 90 is actuated, for example, by a footpedal (not shown) coupled to the compressor or source of compressed gas, gas flows into chamber 103 and through openings 104, mixes with crosslinkable solutions in supply lines 99 and 101, and exits from nozzles 98 and 100. As the gas-solution mixtures emerge from nozzles 98 and 100, they are further atomized and mixed, and directed onto the tissue to be coated. As a result of crosslinking, for example, induced by free radical or chemical crosslinking, the solutions form a film that adheres to the tissue to provide a therapeutic benefit.

The advantages and benefits of the methods and apparatus of the invention are clearly demonstrated by the following example, which is provided for purposes of illustration, and not limitation of the invention. Other such uses will be apparent to those familiar with the art.

Example

Sprayer 10 of FIGS. 1 is used in conjunction with aqueous solutions of crosslinkable monomers. Solution 1, consisting of a 10% solution of a polyethylene glycol diacrylate (M.W. 3,000 Da, purchased from Shearwater Polymers, Huntsville, AL) dissolved in normal saline (pH 5-6) and containing 500 ppm of hydrogen peroxide is drawn up in syringe 13, preferably a 5 cc syringe. Solution 2, consisting of a 10% solution of a polyethylene glycol diacrylate dissolved in normal saline (pH 5-6) and containing 5000 ppm of ferrous sulfate peroxide, is drawn up in syringe

14, also a 5 cc syringe. Syringes 13 and 14 are individually loaded in compartments 23, and are coupled to tubes 24 and 25 and actuator 15.

Airflow from a regulated source of compressed air (an air compressor such as those commercially available for airbrushes) is connected to the sprayer 10 using a piece of tubing. When actuator 15 is depressed, a steady spray of the two liquid components will be observed. When this spray is directed to a piece of tissue a hydrogel coating will be observed to form on the surface of the tissue. The hydrogel coating is resistant to rinsing and is well adhered to the tissue surface. Within a short period of time (less than a minute) an area of 10 cm X 5 cm may be coated with ease.

* * *

While preferred illustrative embodiments of the invention are described above, it will be apparent to one skilled in the art that various changes and modifications may be made therein without departing from the invention and it is intended in the appended claims to cover all such changes and modifications which fall within the true spirit and scope of the invention.

What Is Claimed Is:

1. Apparatus for forming in situ, in a tissue cavity, a tissue adherent coating from at least first and second solutions, the apparatus comprising:

first and second chambers for storing the first and second solutions;

a first nozzle in fluid communication with the first chamber and adapted to permit the first solution to flow from the first nozzle;

a second nozzle in fluid communication with the second chamber and adapted to permit the second solution to flow from the second nozzle;

a first gas flow outlet, the first gas flow outlet disposed surrounding at least the first nozzle; and

a source of pressurized gas coupled to the first gas flow outlet,

wherein pressurized gas exiting the first gas flow outlet atomizes and mixes the first solution with the second solution.

2. The apparatus of claim 1 further comprising a vent hole for venting excess pressure within the tissue cavity.

3. The apparatus of claim 1 further comprising first and second plungers disposed in the first and second chambers, respectively.

4. The apparatus of claim 3 further comprising a member coupling the first and second plungers together.

5. The apparatus of claim 1 wherein gas flowing from the first gas flow outlet induces a venturi effect that draws the first and second solutions from the first and second nozzles, respectively.

6. The apparatus of claim 1 wherein the source of pressurized gas is a compressor.

7. The apparatus of claim 1 wherein the source of pressurized gas is a compressed gas cylinder.

8. The apparatus of claim 1 wherein the first and second chambers are detachably coupled to the first and second nozzles, respectively.

9. The apparatus of claim 1 further comprising means for selectively coupling the source of pressurized gas to the first gas flow outlet.

10. The apparatus of claim 1 further comprising a second gas flow outlet disposed surrounding the second nozzle.

11. The apparatus of claim 1 further comprising means for controlling a rate at which pressurized gas exits the first gas flow outlet.

12. The apparatus of claim 1 further comprising means for regulating a rate at which the first and second solutions flow from the first and second nozzles, respectively.

13. The apparatus of claim 1 further comprising one-way valves that prevent backflow of a pressurized gas from the tissue cavity into the first and second chambers.

14. Apparatus for forming in situ, in a tissue cavity, a tissue adherent coating from at least first and second solutions, the apparatus comprising:

first and second chambers for storing the first and second solutions;

a third chamber coupled to a source of pressurized gas;

a first nozzle coupled to a first supply line, the first supply line being in fluid communication with the first chamber and having an opening in communication with the third chamber; and

a second nozzle coupled to a second supply line, the second supply line being in fluid communication with the second chamber and having an opening in communication with the third chamber,

wherein pressurized gas entering the third chamber enters the first and second supply lines and propels the first and second solutions out of the first and second nozzles, respectively, to atomize and mixes the first solution with the second solution.

15. The apparatus of claim 14 further comprising a vent hole for venting excess pressure within the tissue cavity.

16. The apparatus of claim 14 further comprising first and second plungers disposed in the first and second chambers, respectively.

17. The apparatus of claim 16 further comprising a member coupling the first and second plungers together.

18. The apparatus of claim 14 wherein the source of pressurized gas is a compressor.

19. The apparatus of claim 14 wherein the source of pressurized gas is a compressed gas cylinder.

20. The apparatus of claim 14 wherein the first and second chambers are detachably coupled to the first and second supply lines, respectively.

21. The apparatus of claim 14 further comprising means for selectively coupling the source of pressurized gas to the third chamber.

22. The apparatus of claim 14 further comprising means for regulating a rate at which the first and second solutions flow from the first and second nozzles, respectively.

23. The apparatus of claim 14 further comprising one-way valves coupled between each one of the first chamber and first supply line and the second chamber and the second supply line.

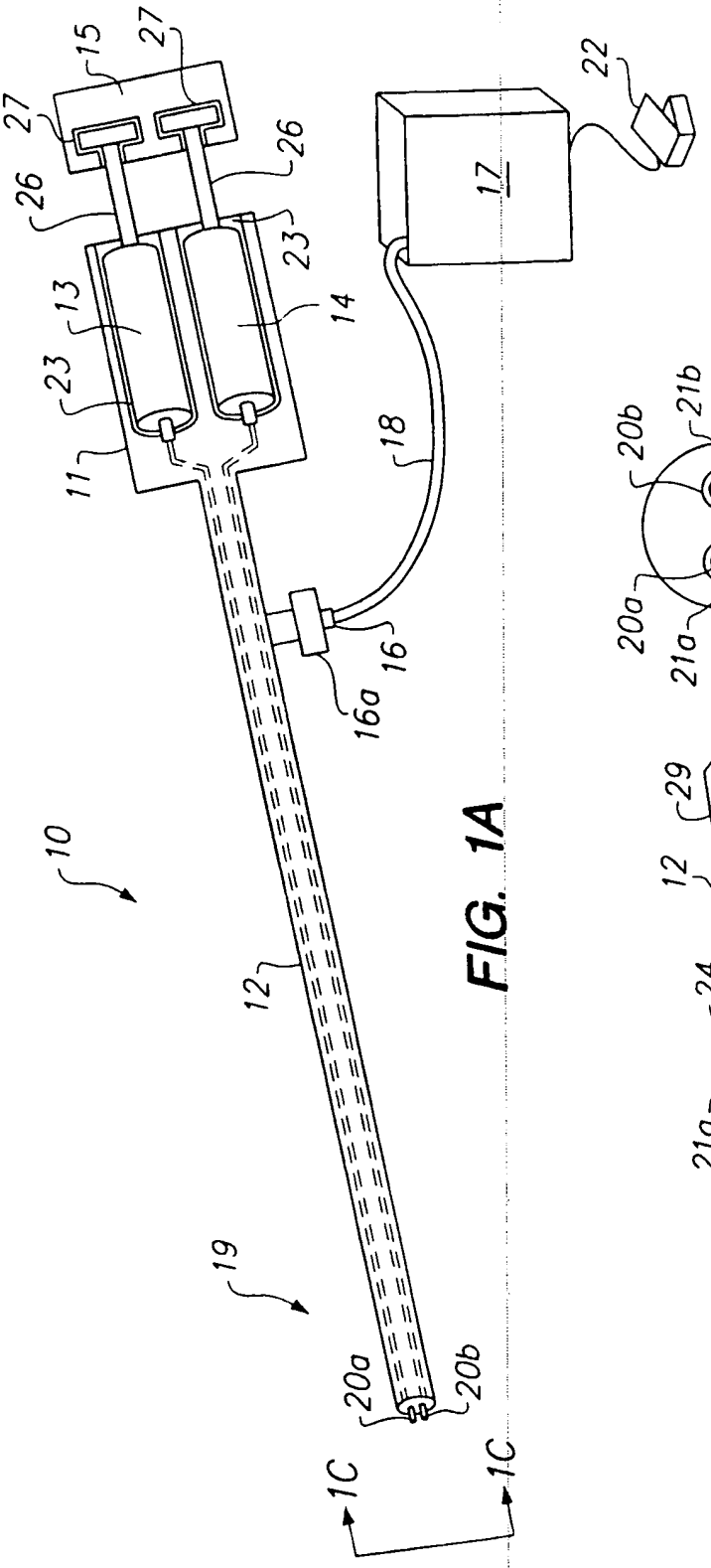

FIG. 1A

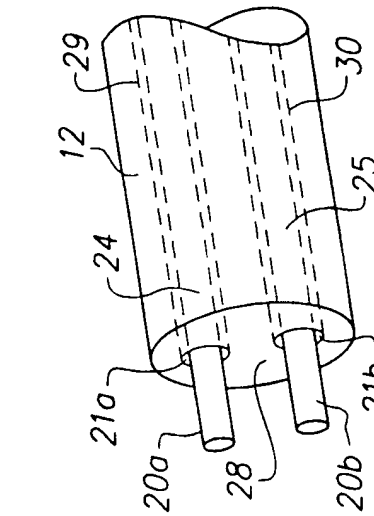

FIG. 1B

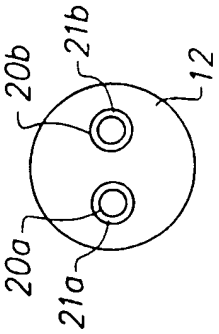

FIG. 1C

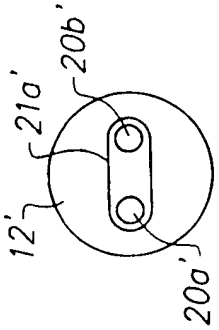

FIG. 1D

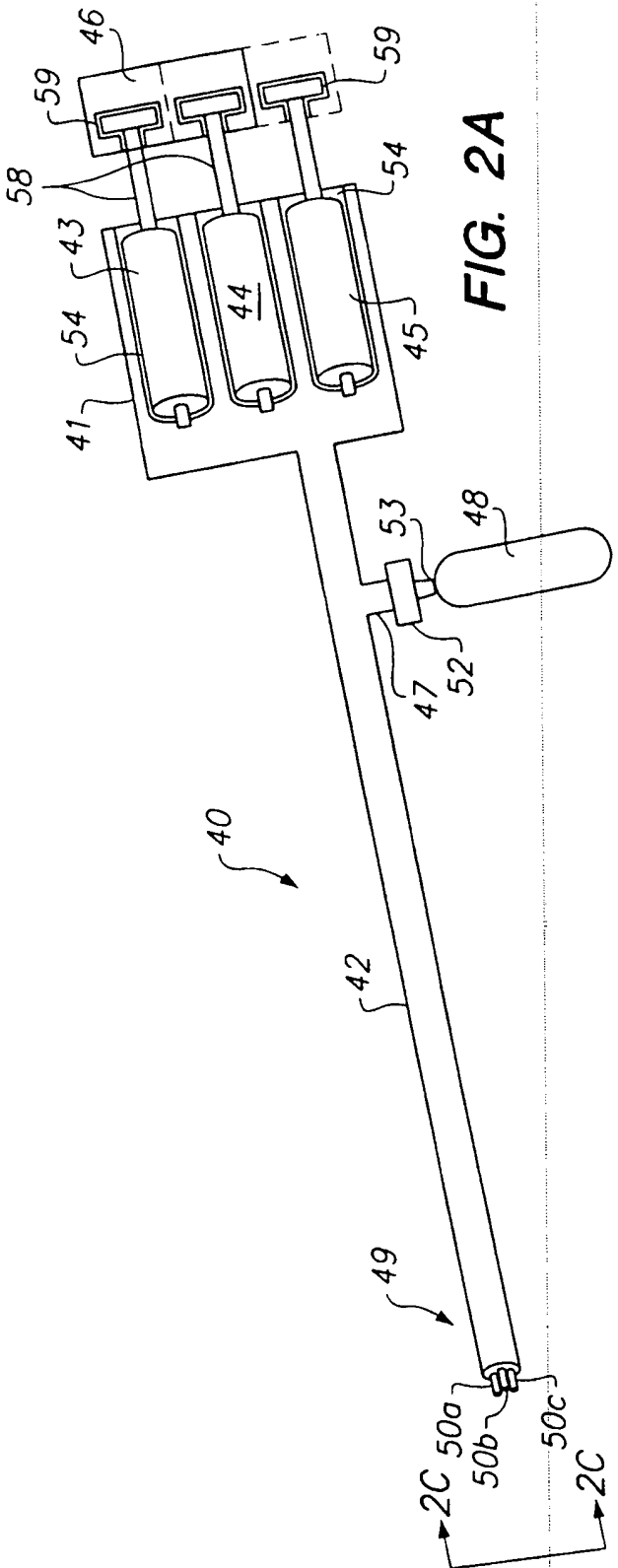

FIG. 2A

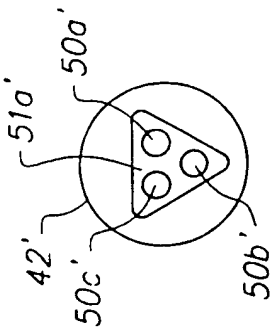

FIG. 2D

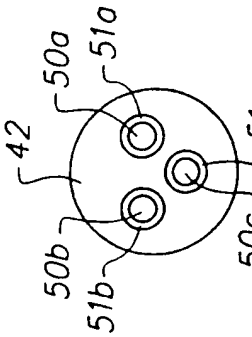

FIG. 2C

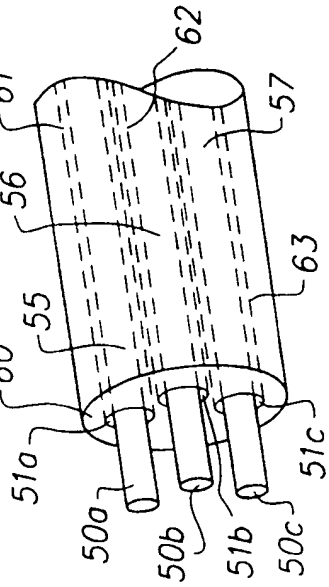

FIG. 2B

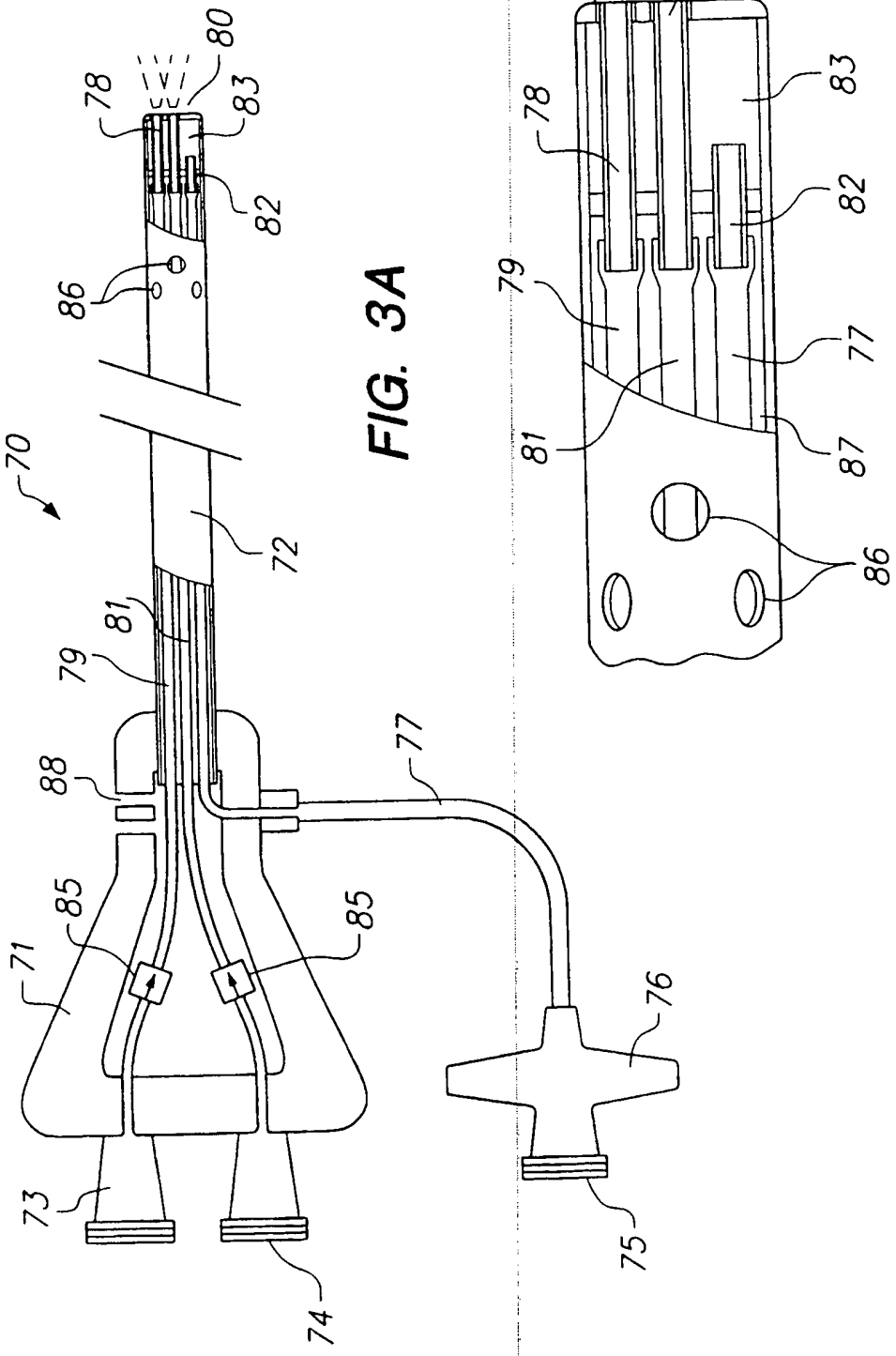

FIG. 3A

FIG. 3B

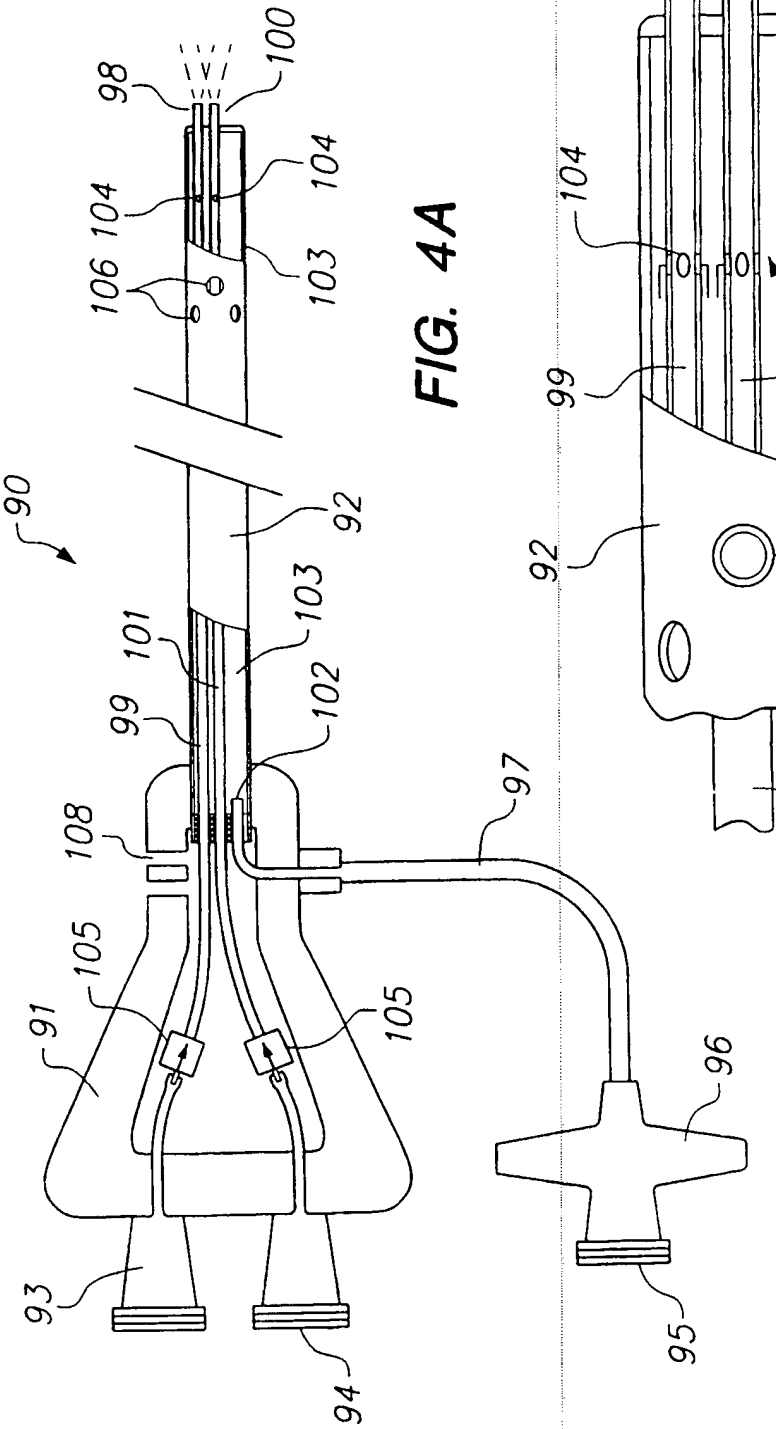

FIG. 4A

FIG. 4B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18446

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61M 37/00
US CL :604/82, 191

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/82-84, 94, 131, 191, 218

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,582,596 A (FUKUNAGA et al.) 10 December 1996, entire document.	1, 3-14, 16-23 --- 2, 15
A	US 5,740,965 A (MIYAGI et al.) 21 April 1998, Abstract.	1-23
A	US 5,759,169 A (MARX) 02 June 1998, Abstract.	1-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 OCTOBER 1999	19 NOV 1999
Name and mailing address of the ISA/US	Authorized officer